DEFINITIVE PRIMARY THERAPY IN PATIENTS PRESENTING WITH OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

Abstract

Background: Although palliative chemotherapy is the standard of care for patients diagnosed with stage IV NSCLC, patients with a small metastatic burden, “oligometastatic” disease, may benefit from definitive local therapy.

Methods: We identified 186 patients (26% of Stage IV patients) prospectively enrolled in our institutional database from 2002-2012 with oligometastatic disease, which we defined as five or fewer distant metastatic lesions at diagnosis. Univariable and multivariable Cox proportional hazards models were used to identify patient and disease factors associated with improved survival. Using propensity score methods, we investigated the effect of definitive local therapy to the primary site on overall survival.

Results: Median age at diagnosis was 61 years, 51% of patients were female, 12% had squamous histology, and 33% had N0-1 disease. On multivariable analysis, ECOG performance status ≥2 (hazard ratio [HR] 2.43), nodal status N2-3 (HR 2.16), squamous pathology, and metastases to multiple organs (HR 2.11) were associated with a greater hazard of death (all $p<0.01$). Number of metastatic lesions and size of primary were not significantly associated with overall survival. Definitive local therapy to the primary tumor was associated with prolonged survival (HR 0.65, $p=0.043$).

Conclusions: Definitive local therapy to the primary tumor appears to be associated with improved survival in patients with oligometastatic NSCLC. Select patient and tumor characteristics, including good performance status, non-

squamous histology, and limited nodal disease, may predict for improved survival in these patients.

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Glossary Listing Abbreviations

AJCC – American Joint Committee on Cancer

BED – Biologically equivalent dose

CI – Confidence interval

Cm(s) – Centimeter(s)

CT – Computed tomography

ECOG – Eastern Cooperative Oncology Group

EGFR – Epidermal growth factor receptor

HR – Hazard ratio

Kg(s) – Kilogram(s)

Mo(s) - Month(s)

MRI – Magnetic resonance imaging

NSCLC – Non-small cell lung cancer

OR – Odds ratio

PET – Positron emission tomography

SBRT – Stereotactic body radiation therapy

SEER – Surveillance, Epidemiology, and End Results program

WBRT – Whole brain radiation therapy

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death in the United States, accounting for approximately 140,000 deaths in 2011.[1] Nearly 40% of patients present with metastatic disease, with median survival 8-10 months even with treatment.[2]

Palliative chemotherapy is considered the standard of care for patients presenting with stage IV non-small cell lung cancer (NSCLC).[2, 3] Of lung and bronchus cancer cases diagnosed from 1996-2004, nearly half were diagnosed after the cancer had already metastasized, termed stage 4 disease.

However, patients with limited metastatic burden – "oligometastatic" disease – may have a better prognosis. For example, one Southwest Oncology Group review including 2531 patients showed that a single metastatic lesion corresponded to an average 1 to 3 month greater survival than multiple metastatic lesions.[4] Some series have shown long-term survivors among those with oligometastatic disease, and therefore many centers may opt to manage this subset of patients with definitive treatment to the primary tumor with the small hope of achieving cure. Furthermore, while older studies have reported that only a small subset (~7%) of patients present with a solitary site of metastatic disease[3], this number in the era of PET-screening is largely unknown.

The definition of oligometastatic disease can vary and has ranged in studies from the presence of a single metastatic lesion to a single organ with multiple metastases to multiple lesions in multiple organs.[5-7] These definitions can limit the number of participants involved in a study. For example, one single-institution series from a database of 1509 patients with metastatic NSCLC who underwent surgery to the primary identified only ten patients with a synchronous solitary hematogenous metastasis, defined as a metastasis present upon diagnosis of the primary tumor.[5] Staging workup consisted of a comprehensive body CT scan, magnetic resonance imaging (MRI) in the case of suspected brain metastases, and total body positron emission tomography (PET) scan. In contrast, another retrospective study from a database of 169 patients who underwent diagnostic or therapeutic surgical procedures for metastatic lung cancer identified 29 patients with a single organ of metastatic disease.[6] The definition of oligometastatic disease in many of these studies has been derived tautologically from patients treated aggressively. Thus, an objective criteria for oligometastatic disease is lacking.

However, recent series have allowed patients with up to five discrete metastatic lesions total to be included in the definition of oligometastatic disease.[8-10] Though several studies have reported favorable outcomes with the use of definitive local therapy in oligometastatic NSCLC, many are limited to single-institution studies that compare results to historical controls.[7, 8, 11, 12] Select series have found one-year overall survivals ranging from 65% to 74% for patients with oligometastatic disease receiving complete surgical resection of the primary tumor[6, 7, 13], and

54% to 62% for patients receiving chemoradiation with curative intent to the primary site.[8, 14, 15] ENREF 11 However, these results are likely biased by the tumor characteristics of the patients selected. Surgical series have required potentially resectable primary disease in the chest and focused on patients with primarily brain metastases[6, 16], while chemoradiation studies have included patients with primary tumors not considered surgically resectable and metastatic sites such as bone that are not ordinarily resected.[8, 15]

Small case series have shown that for individuals with favorable risk factors, for example good performance status and limited weight loss, aggressive therapy – including surgery, chemotherapy, and/or radiation – to the primary tumor may result in prolonged survival.[7, 17-19] One large retrospective study of 78 patients with five or fewer metastatic lesions who were treated with chemoradiation therapy showed increased overall survival and reduced tumor burden in patients who received high-dose primary radiotherapy and received definitive local metastatic treatment compared to historical controls.[8] Another study of 29 patients with a single organ with metastatic disease treated with surgery to the primary site demonstrated median survival of 20.5 months, with one- and five-year survivals of 65% and 36%, respectively.[6] Finally, a surgical series of 53 patients with oligometastatic NSCLC who were treated with curative surgery demonstrated median overall survival of 19 months, with one- and five-year survivals of 73% and 24%, respectively.[20] While these survival rates all compare favorably to historical controls, it is again important to note that these series involved highly selected individuals and lacked a control group. Thus, it is difficult

to draw definitive conclusions about the benefit of definitive therapy from these studies.

Other favorable mediators of survival in NSCLC exist as well.[2] Survival may further depend on patient and tumor characteristics, such as metastatic site: for example, retrospective reviews suggest that median survival even with aggressive treatment may differ between solitary synchronous brain (7-24 mos)[13, 21, 22] and adrenal (11-31 mos)[23, 24] metastases. For example, five-year survival rates in NSCLC based on data from 13 SEER sites are greater for females vs. males (20.0% vs. 14.8%), whites vs. blacks (17.8% vs. 14.5%), and age < 65 vs. age > 65 (20.2% vs. 15.6%). Overall, this suggests that even within oligometastatic disease, survival likely depends heavily on other demographic factors and tumor characteristics.

While these series suggest that patients with oligometastatic disease may have prolonged survival with definitive surgery or chemoradiation, there have been no randomized comparisons of definitive versus palliative management of these patients. Furthermore, nearly all of these retrospective series have included highly selected groups of patients who had favorable risk factors, for example good performance status and limited weight loss, who might also be expected to do relatively well with palliative therapies. Therefore, it is not clear whether patient outcomes would have differed significantly if these patients had been managed with only palliative measures upfront. Moreover, aggressive therapies in patients with “incurable” cancers can be associated with emotional, financial,

and quality-of life costs in the face of uncertain benefits.[25, 26] This is important because all retrospective studies of patients with oligometastatic NSCLC have focused on survival as the primary outcome. No comparative effectiveness study on treatment for oligometastatic NSCLC exists that factors quality of life after treatment. Thus, studies that suggest the benefit of definitive therapy may not capture the full consequence of therapy.

In the absence of randomized data, retrospective comparisons of patients presenting with oligometastatic NSCLC managed with or without definitive local therapy can provide additional information regarding which patients may benefit most from definitive treatment to the primary tumor. Furthermore, such evidence comparing patients managed with or without definitive local therapy would provide important insight into the argument for aggressive local therapy in oligometastatic NSCLC and may address the significant selection bias that exists in previous retrospective analyses. The purpose of this retrospective cohort analysis is to compare survival outcomes in patients with oligometastatic NSCLC who receive definitive local therapy to the primary tumor vs. patients with oligometastatic NSCLC who do not receive definitive local therapy. Using a cohort of patients diagnosed with metastatic NSCLC presenting to the Thoracic Oncology Program at the Dana-Farber Cancer Institute from 2002 to 2012 with a minimum of one year of follow-up, we identified patients who presented with oligometastatic disease at diagnosis and compared survival outcomes among patients who received and did not receive definitive local therapies. We

furthermore identified patient and disease factors that were associated with prolonged survival among patients with oligometastatic NSCLC.

Methods

Study cohort

We identified patients presenting with stage IV NSCLC (AJCC 7th edition) who consented and were prospectively enrolled in our institutional database from 2002 to 2012 within 12 months after diagnosis. Inclusion criteria included stage IV disease at diagnosis, sufficient radiologic and/or pathologic records at presentation to determine tumor stage, sufficient follow-up records to determine treatment, no prior radiation therapy, and no history of prior malignancy other than successfully treated skin cancer. All patients provided written informed consent and the investigation was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board.

Identification of oligometastatic disease

We defined oligometastatic disease as five or fewer total discrete distant metastatic lesions involving any organ system visualized on PET-CT and/or MRI of the brain at the time of initial staging. Recent series have identified patients with this definition of oligometastatic disease as potentially eligible for high-dose radiation to the primary site of cancer.[8, 9] ENREF 12

Definition of key variables

The primary outcome variable was overall survival, which was defined as the time from date of pathological diagnosis to date of death or last follow-up.[27, 28]

Key covariates included patient, disease, and treatment characteristics. Patient characteristics included age in years (<65, ≥65), gender (male, female), race (white, non-white), ECOG performance status (0-1, 2+), weight loss in the six months prior to diagnosis (≤10%, >10%) and smoking history (never/former, current smoker). Smoking information was prospectively collected by self-report. A never smoker was defined as a person who smoked fewer than 100 cigarettes in their lifetime and a former smoker was defined as a person who had quit one year or longer before their diagnosis. Disease characteristics included tumor size (≤3 cm, >3cm), nodal spread of disease (N0-1, N2-3), organ sites with metastatic involvement (brain, bone, adrenal, other single site, multiple sites), pathology (non-squamous epidermal growth factor receptor (EGFR) wild type or unknown, non-squamous EGFR activating mutation, squamous) and number of metastatic lesions (1, 2, 3-5). Treatment characteristics examined included use of aggressive local therapy to primary and metastatic sites. We defined aggressive local therapy of primary disease as either surgical resection and/or definitive radiation of biological equivalent dose (BED10 without time adjustment) ≥53 or stereotactic body radiation therapy (SBRT) to the primary tumor. We defined aggressive local therapy of metastatic disease as surgical resection and/or definitive radiation (BED ≥53, whole brain radiation therapy [WBRT], stereotactic radiosurgery [SRS], or SBRT) to all known sites of metastatic disease.

Statistical methods

Overall survival among patients diagnosed with oligometastatic versus more extensive disease was compared using univariable Cox proportional hazards regression. Because our institutional database only began to enroll all patients with lung cancer diagnoses starting in 2009 (prior to this date, most patients were selectively enrolled for specific projects based on likely genomic characteristics), survival comparisons between these cohorts were made only for those diagnosed in 2009 and after.

Among patients diagnosed with oligometastatic disease from 2002-2012, univariable and multivariable Cox proportional hazards models with backward selection were used to analyze patient and disease factors associated with overall survival. Univariable associations between patient and disease factors with receipt of definitive local therapy were assessed using Fisher's exact test. To evaluate the association between definitive local therapy and overall survival, propensity score analyses were performed using inverse probability weights to balance measurable confounders between those who did and did not receive definitive treatment; all variables described in Table 1 were used to calculate the patient's propensity to receive definitive treatment, regardless of statistical significance.[29, 30]

P values were two-sided and values <0.05 were considered statistically significant. Patients with missing values for any of the key covariates were excluded from analyses that used those specific variables. All analyses were performed using Stata (version 11.2) software (Stata Corp LP, College Station, Texas).

Results

We identified 725 patients diagnosed with NSCLC who satisfied our inclusion criteria. Of these, 186 patients (26%) had oligometastatic disease at diagnosis and 539 patients (74%) had more extensive disease. Figure 1 summarizes our study cohort.

Overall survival among patients with oligometastatic versus more extensive disease

Among 423 patients diagnosed with metastatic lung cancer between 2009-2012, 19% had oligometastatic disease, which we defined as five or fewer discrete lesions. Median survival was 17 months versus 14 months for patients with versus without oligometastatic disease (hazard ratio 0.73, 95% CI 0.53-1.01, p=0.054, see Figure 2).

Factors associated with survival for patients with oligometastatic NSCLC

Among 186 patients diagnosed with oligometastatic lung cancer between 2002-2012, there were 140 deaths. The median follow-up for survivors was 24 months. Median age at diagnosis was 61 years, 51% of patients were female, 12% had squamous histology, and 33% had N0-1 disease. 38% had brain metastases, 41% had bone metastases, and 80% had a single organ involved with one or

more metastases. 52% had a single metastatic lesion in a single metastatic site. Baseline patient characteristics are summarized in Table 1.

Overall, 9% of patients received aggressive treatment to the primary tumor only, 17% to metastatic sites only, 20% to both primary and metastatic sites, and 54% to neither site. Preliminary unadjusted analyses indicated that patients who received aggressive local treatment to either the primary tumor only (HR 0.64, 95% CI 0.33-1.24, p=0.189) or to both primary tumor and metastatic sites (HR 0.59, 95% CI 0.37-0.95, p=0.029) had improved survival compared to patients who received either aggressive treatment to the metastatic sites only or no aggressive treatment (see Table 2). Therefore, definitive primary treatment was defined as aggressive treatment to the primary tumor with or without aggressive treatment to the metastatic sites. Patients with fewer metastatic lesions and lower nodal stage were significantly more likely to receive definitive treatment. Site of metastasis was also associated with receipt of definitive treatment (in reference to brain-only metastases: odds ratio [OR] 0.15 for bone-only metastases, OR 0.34 for adrenal-only metastases, OR 0.34 for other single-site metastases, and OR 0.10 for multiple sites of metastases; global p<0.001); 54% of patients with brain-only metastases received definitive treatment, while 15% with bone-only metastases and 11% with metastases in multiple organs received definitive primary therapy.

Table 3 contains results of univariable and multivariable analyses to determine associations between clinicopathologic characteristics and overall survival. On

multivariable analysis, ECOG performance status ≥2 vs <2 (HR 2.43, 95% CI 1.39-4.25, p=0.002), nodal status N2-3 vs N0-1 (HR 2.16, 95% CI 1.43-3.28, p<0.001), pathology (in reference to non-squamous EGFR wild-type: HR 1.97 [95% CI 1.14-3.40] for squamous, and HR 0.46 [95% CI 0.25-0.85] for non-squamous EGFR activating; overall p=0.001), and having more than one metastatic organ involved (HR 2.11, 95% CI 1.36-3.26, p=0.001) were significantly associated with overall survival. As shown in Table 4, site of metastatic disease was not associated with overall survival after controlling for number of metastatic organs, as all hazard ratio confidence intervals were overlapping.

Propensity score analysis of definitive versus nondefinitive primary treatment

The median overall survival was 19 months (95% CI 13 to 34 months) for patients who received definitive primary treatment versus 16 months (95% CI 13 to 19 months) for patients who did not receive definitive treatment. The unadjusted hazard ratio for death associated with definitive treatment was 0.62 (95% CI 0.42 to 0.93, p=0.019). After propensity score adjustment with inverse probability weights, the adjusted hazard ratio associated with definitive treatment was 0.65 (95% CI 0.43 to 0.99, p=0.043). Additional analyses using alternative propensity score methodologies confirmed the favorable survival for patients receiving definitive treatment, with adjusted hazard ratios ranging from 0.68 to 0.73. As shown in Table 5, propensity score matching removed significant demographic risk factor differences between patients receiving definitive versus

non-definitive therapy. Thus, we can be reasonably confident in the results of our head-to-head comparison of overall survival between patients receiving and not receiving definitive therapy.

Discussion, Conclusions, and Suggestions for Future Work

Discussion and Conclusions

Stage IV NSCLC is associated with low survival; however, patients diagnosed with oligometastatic disease may have a better prognosis than those with more extensive disease. Several small case series have suggested improved outcomes with definitive treatment to the primary tumor in oligometastatic disease.[7, 11, 17, 18] Our study provides further comparative evidence of a survival benefit of definitive therapy to the primary tumor in patients with oligometastatic disease, using a control group of patients with oligometastatic disease who did not receive definitive primary therapy.

Patients in our cohort with oligometastatic NSCLC at diagnosis had greater overall survival compared to those with more extensive stage IV disease (median 17 months versus 14 months). This three-month survival difference is similar to what has been reported in a previous analysis of Southwest Oncology Group trials, which showed a 3.6-month and 20% one-year survival improvement in patients with a single metastatic lesion compared to those with multiple metastatic lesions.[4]

Among patients with oligometastatic disease, defined as five or fewer lesions, we identified several factors associated with improved survival, including better performance status, lower nodal stage, non-squamous pathology , and fewer

metastatic organs involved. Many of these factors have been described in the literature as positive prognostic factors in oligometastatic NSCLC. [8, 13, 31] Interestingly, low number of metastatic lesions and small radiologic size of the primary tumor, which have been associated with favorable progression-free survival in other case series, were not significantly associated with longer overall survival in our cohort.[8, 9, 32] Fewer discrete metastatic lesions in patients with oligometastatic NSCLC has been associated with improved progression-free survival in other retrospective case series[9, 32], as has tumor volume.[8] The discrepancy in findings between these studies and ours is likely explained by the fact that previous studies have included only patients with metastases amenable to definitive treatment, whereas our study looked at all patients with oligometastatic disease, regardless of treatment received.

Previous large case series have evaluated the use of definitive local treatment to the primary tumor in oligometastatic disease. In particular, one large retrospective study of 78 patients with less than five metastatic lesions who were treated with high-dose radiotherapy to the primary tumor showed one- and three-year overall survival rates of 62% and 25%, respectively.[8] Another two-institution study of 61 patients with one to three synchronous metastatic lesions treated with surgical resection and/or definitive radiation to all sites of disease showed one- and two-year overall survival of 54% and 38%, respectively.[14] One prospective phase II trial of 40 patients with less than five metastatic lesions demonstrated one-, two-, and three- year overall survival rates of 56%, 23%, and 18%, respectively.[15] Although these studies suggest that favorable outcomes can be

achieved with definitive local therapy, they lacked a comparator group of patients with oligometastatic disease who were not definitively managed. Thus, the external validity of these studies remains in question.

Propensity score adjustment provides a useful way to account for relevant covariates and to control for possible selection bias due to observed confounders between patients who received definitive versus palliative therapy. In essence, propensity score matching attempts to reduce bias due to confounding in observational studies by attempting to mimic randomization. Propensity matching achieves this by creating a sample in the experimental group that is comparable on all observed covariates to the control group.

A key advantage of propensity score matching is that it attempts to control for a number of covariates between the control and experimental group (see Table 5). Our propensity score analyses suggested that definitive treatment of patients with oligometastatic NSCLC conferred a survival benefit to patients with oligometastatic NSCLC. Site of oligometastatic disease (e.g. brain, bone, adrenal) was not independently associated with overall survival, although patients with brain-only metastases were more likely to receive definitive therapy.

There are several limitations to this study. No retrospective analysis can replace a properly conducted randomized trial. Therefore these results should be interpreted with caution. Although we adjusted for propensity to receive definitive local therapy based on observed patient characteristics, propensity scores

cannot adjust for unobserved characteristics. It is possible that patients receiving definitive local therapy were more likely to have additional favorable characteristics that we could not control for. In the absence of a randomized study, however, retrospective analyses can inform clinical decision-making and provide the basis for future randomized comparisons.

Additionally, while our single-institution database began enrolling some patients in 2002, the database did not enroll all patients with lung cancer diagnoses until 2009. Therefore, data for patients enrolled between 2002 and 2009 may have selection bias. We attempted to control for this by only conducting survival comparisons in cohorts diagnosed after 2009. We additionally addressed confounding through propensity score adjustments.

The median survival of non-oligometastatic patients in our study (14 months) is higher than that reported in historical controls.[2] This is likely due to the patient cohort seen at our institution, which tends to be younger and with a higher proportion of white, female, and non-smoking patients than the general population of patients diagnosed with lung cancer.[2, 33]

Finally, our study was not powered to assess different methods of definitive treatment and thus could not compare the effects of surgery versus radiation to the primary tumor. This study was also not powered to detect the mediating effects of patient and tumor characteristics on the efficacy of definitive treatment. Overall survival may depend on patient and tumor characteristics such as

metastatic site: for example, retrospective reviews suggest that median survival even with definitive treatment may differ between solitary synchronous brain (7-24 mos)[13, 21, 22] _ENREF_20 and adrenal (11-31 mos)[23, 24] metastases.

Future Directions

The results of this retrospective cohort study should be further assessed with a prospective randomized trial to assess the benefit of definitive treatment in oligometastatic NSCLC. A randomized trial is the goal standard for effectiveness; however, this may be difficult to perform in this population, as treatment choice is highly influenced by patient and physician preference. Nevertheless, there is precedent for a randomized trial comparing primarily supportive therapy vs. primarily aggressive therapy (e.g. chemotherapy) in stage IV NSCLC.[34] Furthermore, a randomized trial would address the likely unmeasured variables that are potentially biasing the results in this study.

Additional analyses should investigate the role of different definitive therapies for oligometastatic disease. Our study was underpowered to compare surgery versus radiation for aggressive treatment of metastatic NSCLC. As mentioned above, case series in patients with oligometastatic NSCLC who receive definitive surgery or radiation to the primary tumor have showed comparable one-year survival rates between 50-75%. However, there has never been a prospective comparison between the two treatment modalities. Current NCCN guidelines for a solitary brain or adrenal metastasis with limited chest-only stage list both

surgical resection and stereotactic ablative radiotherapy of the lung lesion as potential treatment options.[35] A prospective randomized comparison between surgery and radiation for oligometastatic NSCLC would also address the significant selection bias that exists in retrospective case series of patients treated with primary surgery or radiotherapy, as candidates for surgery are likely to have different patient and tumor characteristics compared to candidates for radiotherapy.

Additionally, as definitive local therapy may be associated with significant cost and quality of life implications, a comparative effectiveness study should be performed that takes into account toxicity and utility of the various interventions. For example, chest radiotherapy can be associated with short-term (e.g. pneumonitis, swallowing difficulties) and long-term effects (e.g. reduction in pulmonary function) that could impact quality of life.[36] A comparative effectiveness study, such as a decision analysis/Markov model, could take into account toxicity rates and utilities that have been reported in prior case studies to compare different treatments.[37, 38]

Finally, additional observational studies could investigate the role of definitive treatment to the primary tumor for oligometastatic recurrence of initially localized disease, for which some evidence of efficacy exists. For example, one thirteen-person study, showed that definitive treatment for oligometastatic recurrence of previously resected NSCLC resulted in progression-free survivals of 20 months.[39] This suggests that definitive local treatment could be a first-line treatment

strategy for patients with oligometastatic recurrence of disease. A prospective trial comparing patients with oligometastatic NSCLC recurrence who receive definitive local therapy versus those who do not is thus certainly necessary.

Summary

In conclusion, patients with oligometastatic non-small cell lung cancer may have improved survival with definitive local therapy; however, prior retrospective analyses have based this conclusion on data from historical controls. This study suggests that definitive treatment to the primary tumor may confer a survival benefit in patients with oligometastatic NSCLC. Furthermore, factors such as nodal involvement, pathology, and patient performance status may also influence survival and should also be considered in the decision to pursue definitive treatment for these patients. This study is limited by its reliance on observational data and therefore should be considered hypothesis-generating rather than definitive. Future prospective studies should be performed to provide more definitive evidence regarding the effect of definitive local therapy in NSCLC.

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Figure Legend

Figure 1. Study cohort.

Figure 2. Overall survival stratified by presence of oligometastatic disease, among patients diagnosed 2009-2012.

Figure 1. Study cohort

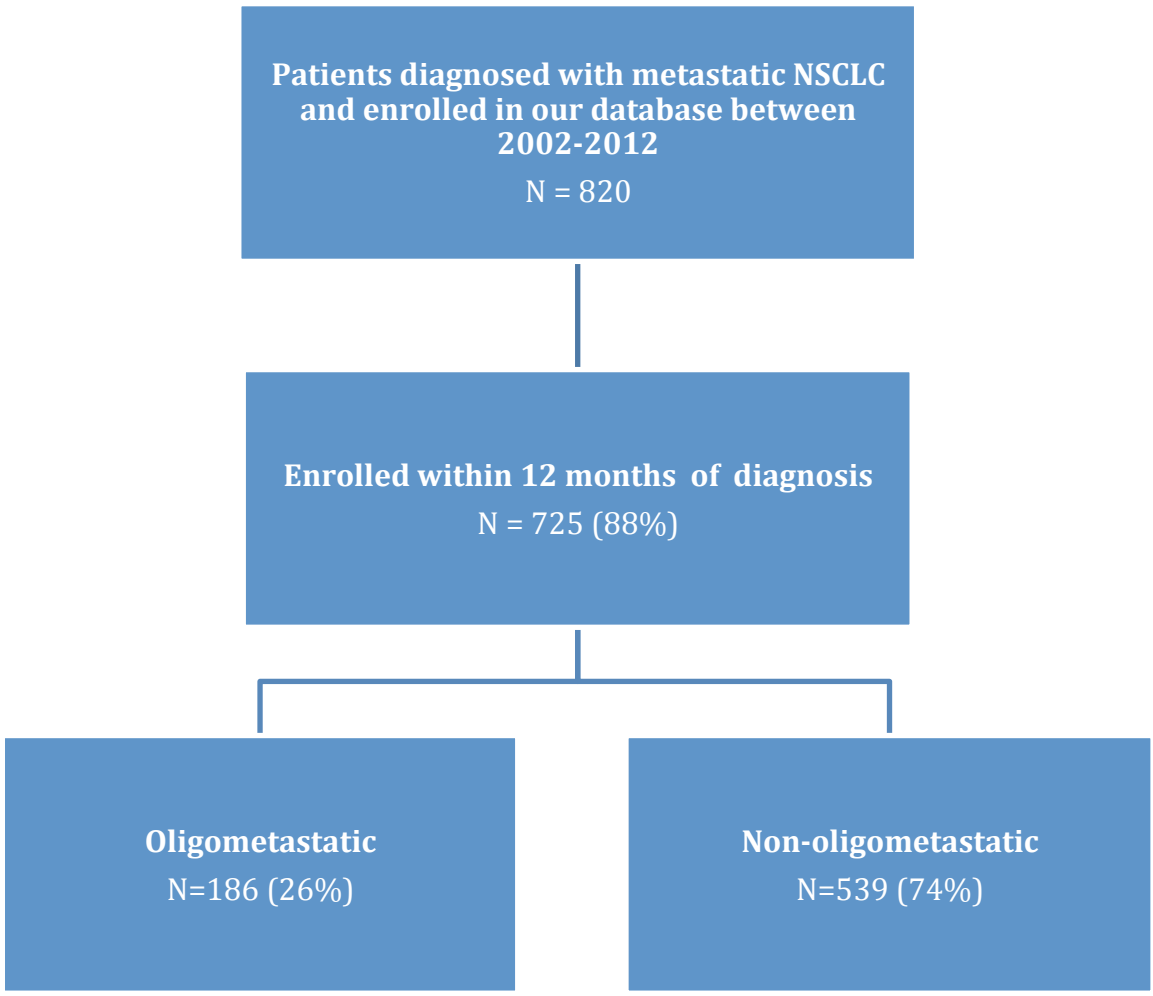

Figure 2. Overall survival stratified by presence of oligometastatic disease, among patients diagnosed 2009-2012.

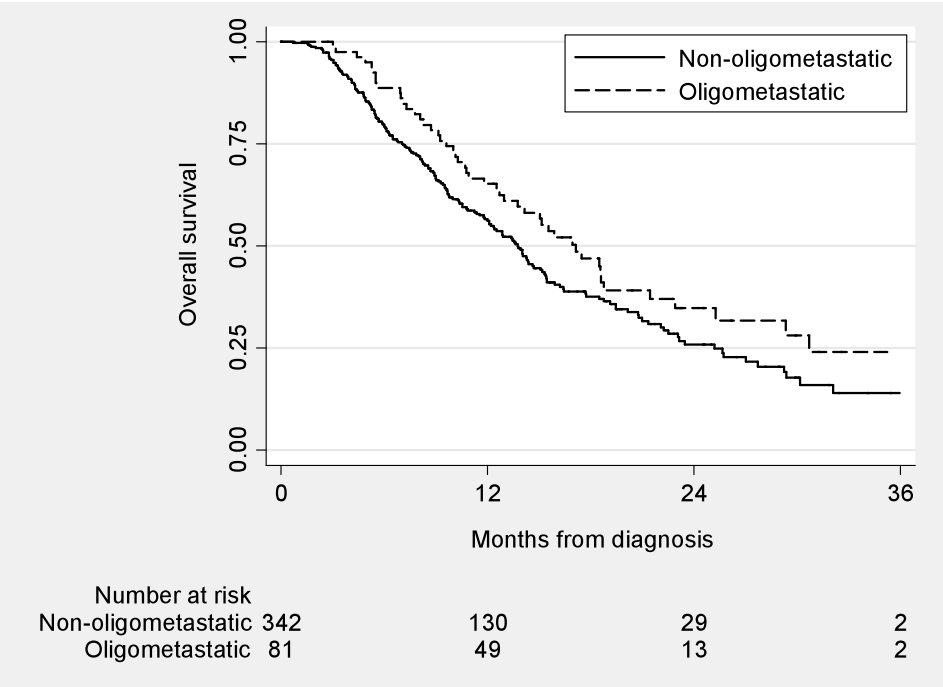

Table 1. Characteristics of patients diagnosed with oligometastatic disease between 2002 and 2012, overall and stratified by whether the patient received definitive treatment to the primary tumor. Hazard ratios > 1 represent lower overall survival.

	Overall	Definitive Treatment		P Value
		No	Yes	
Number of patients	186 (100)	133 (72)	53 (28)	
Age (years)				0.065
<65	116 (62)	77 (66)	39 (34)	
≥65	70 (38)	56 (80)	14 (20)	
Gender				0.144
Male	92 (49)	61 (66)	31 (34)	
Female	94 (51)	72 (77)	22 (23)	
Race (N=181)				0.507
White	170 (94)	123 (72)	47 (28)	
Non-white	11 (6)	7 (64)	4 (36)	
Smoking history (N=185)				0.722
Never or former smoker	132 (71)	93 (70)	39 (30)	
Current smoker	53 (29)	39 (74)	14 (26)	
ECOG performance status				0.088
1 or lower	162 (87)	112 (69)	50 (31)	
2 or higher	24 (13)	21 (88)	3 (13)	
Weight loss (in 6 months before diagnosis)				0.643
≤ 10%	161 (87)	116 (72)	45 (28)	
> 10%	25 (13)	17 (68)	8 (32)	
Radiologic size of primary tumor (N=184)				0.504
≤ 3.0cm	71 (39)	53 (75)	18 (25)	
> 3.0cm	113 (61)	78 (69)	35 (31)	
Nodal status (N=185)				0.037
N0-N1	61 (33)	37 (61)	24 (39)	
N2-N3	124 (67)	95 (77)	29 (23)	
Pathology				0.323
Non-squamous, EGFR wild-type or unknown	144 (77)	104 (72)	40 (28)	
Non-squamous, EGFR activating	20 (11)	16 (80)	4 (20)	
Squamous	22 (12)	13 (59)	9 (41)	
Number of metastatic lesions				0.026
1	97 (52)	63 (65)	34 (35)	
2	40 (22)	28 (70)	12 (30)	
3 to 5	49 (26)	42 (86)	7 (14)	
Metastatic site				<0.001
Brain only	54 (29)	25 (46)	29 (54)	
Bone only	53 (28)	45 (85)	8 (15)	
Adrenal only	14 (8)	10 (71)	4 (29)	
Other single site	28 (15)	20 (71)	8 (29)	
Multiple sites	37 (20)	33 (89)	4 (11)	

ECOG = Eastern Cooperative Oncology Group; kg = kilograms; cm = centimeters

Table 2. Unadjusted association between treatment and overall survival among patients with oligometastatic disease. Hazard ratios > 1 represent lower overall survival.

Treatment	Number of patients (%)	Hazard Ratio	95% CI	P Value
No aggressive treatment	101 (54)	1.00	--	--
Yes: to metastatic sites only	32 (17)	0.90	0.57 to 1.41	0.647
Yes: to primary tumor only	16 (9)	0.64	0.33 to 1.24	0.189
Yes: to both metastatic sites and primary tumor	37 (20)	0.59	0.37 to 0.95	0.029

Table 3. Univariable and multivariable Cox proportional hazards regression to determine associations between clinicopathologic characteristics and overall survival, among patients with oligometastatic disease.

	Univariable			Multivariable† (N=177)		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Age (years)			0.587			
<65	Reference			Reference		
≥65	0.91	0.64 to 1.28		0.76	0.52 to 1.12	0.162
Gender			0.945			
Male	Reference			Reference		
Female	0.99	0.71 to 1.38		0.85	0.59 to 1.24	0.406
Race			0.793			0.092
White	Reference			Reference		
Non-white	0.90	0.42 to 1.94		0.49	0.22 to 1.12	
Smoking history			0.440			
Never or former smoker	Reference			--	--	--
Current smoker	1.16	0.80 to 1.67		--	--	--
ECOG performance status			<0.001			0.002
1 or lower	Reference			Reference		
2 or higher	2.42	1.51 to 3.88		2.43	1.39 to 4.25	
Weight loss			0.011			
≤ 10%	Reference			--	--	--
> 10%	1.84	1.15 to 2.93		--	--	--
Radiologic size of primary tumor			0.793			
≤ 3.0cm	Reference			--	--	--
> 3.0cm	1.05	0.74 to 1.48		--	--	--
Nodal status			0.001			<0.001
N0-N1	Reference			Reference		
N2-N3	1.91	1.30 to 2.80		2.16	1.43 to 3.28	
Pathology			0.003			0.001
Non-squamous, EGFR wild-type or unknown	Reference			Reference		
Non-squamous, EGFR activating	0.50	0.28 to 0.89		0.46	0.25 to 0.85	
Squamous	1.67	1.01 to 2.77		1.97	1.14 to 3.40	
Number of metastatic lesions			0.727			
1	Reference			--	--	--
2	1.11	0.73 to 1.69		--	--	--
3 to 5	1.17	0.78 to 1.74		--	--	--
Number of metastatic sites‡			<0.001			0.001
1	Reference			Reference		
2 to 3	2.33	1.58 to 3.45		2.11	1.36 to 3.26	

† Age, gender, and stage were forced into the multivariable model. Inclusion of other variables in the model was determined by using a backwards selection procedure, with the significance level of being removed from the model set at 0.10.
‡ Site of metastasis (brain, bone, adrenal, or other) was not significantly associated with overall survival, after controlling for number of metastatic sites (all p>0.16).
ECOG = Eastern Cooperative Oncology Group; kg = kilograms; cm = centimeters

Table 4. Hazard ratios for overall survival based on site of disease.

Site of disease	Hazard Ratio for aggressive treatment to primary tumor (yes vs no)	95% CI
Brain only	0.66	0.34 to 1.27
Bone only	0.64	0.25 to 1.65
Adrenal only	0.70	0.18 to 2.66
Other single site	0.43	0.12 to 1.49
Other multiple sites	0.76	0.26 to 2.19

Table 5. Comparison of patient characteristics among patients receiving aggressive versus non-aggressive treatment, after propensity score matching

	Definitive Treatment		Exact P Value
	No (N=49)	Yes (N=49)	
Age (years)			1.00
<65	37 (51)	36 (49)	
≥65	12 (48)	13 (52)	
Gender			1.00
Male	28 (49)	29 (51)	
Female	21 (51)	20 (49)	
Race			1.00
White	45 (50)	45 (50)	
Non-white	4 (50)	4 (50)	
Smoking history			1.00
Never or former smoker	35 (49)	36 (51)	
Current smoker	14 (52)	13 (48)	
ECOG performance status			1.00
1 or lower	47 (51)	46 (49)	
2 or higher	2 (40)	3 (60)	
Radiologic size of primary tumor			0.69
≤ 4.0cm	27 (53)	24 (47)	
> 4.0cm	22 (47)	25 (53)	
Nodal status			1.00
N0/N1	22 (49)	23 (51)	
N2/N3	27 (51)	26 (49)	
Pathology			0.67
Non-squamous, EGFR- or unk	40 (52)	37 (48)	
Non-squamous, EGFR+	4 (50)	4 (50)	
Squamous	5 (38)	8 (62)	
Number of metastatic lesions			0.82
1	34 (52)	32 (48)	
2	9 (43)	12 (57)	
3 to 5	6 (55)	5 (45)	
Metastatic site			0.39
Brain only	17 (40)	26 (60)	
Bone only	11 (61)	7 (39)	
Adrenal only	7 (64)	4 (36)	
Other single site	11 (58)	8 (42)	
Other multiple sites	3 (43)	4 (57)	